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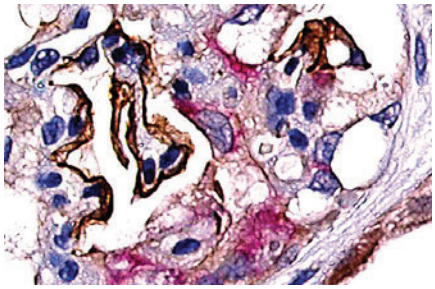
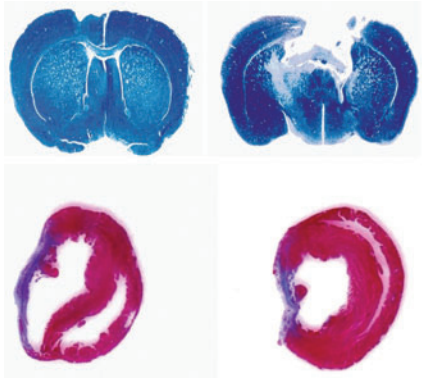
Parietal epithelial cell proliferation in collapsing FSGS



There is good evidence that podocytes are lost in focal segmental glomerulosclerosis (FSGS), a mechanism that has been given a central role in the pathogenesis of this disease. However, in the collapsing variety of FSGS (often seen in HIV nephropathy), hyperplasia of glomerular epithelial cells is seen. In a new article, Dijkman *et al.* address the question of which cells are proliferating. Studies on patients with HIV nephropathy and pamidronate nephropathy showed that the proliferating cells expressed markers of parietal glomerular epithelial cells rather than those of podocytes. Recent studies have characterized a large number of proteins that are specifically expressed in the podocytes, such as synaptopodin, vascular endothelial growth factor, and CD10, and others are expressed in the parietal epithelial cells, such as CK8 and PAX2. The proliferating cells identified with simultaneous staining for a proliferation marker and cell type-specific epithelial protein showed that the proliferating cell expressed the parietal but not the podocyte markers. Also, the matrix deposited by these cells stained identically to that of Bowman's capsule. Thus, one previous explanation for the origin of the proliferating cell — dedifferentiated podocytes — seems to have been ruled out by these studies. **See page 338**.

Local erythropoietin and tissue injury

The role of erythropoietin (EPO) in regulating red-cell mass is now accepted as a scientific and therapeutic reality, but there is increasing evidence that the kidney is not its sole site of production nor the erythroid marrow its only target of action. In this issue, Brines and Cerami review this exciting frontier of research. They show that EPO is produced locally by many tissues in response to injury. In particular, they discuss ischemic preconditioning,



a phenomenon whereby previous exposure to brief periods of ischemia seems to protect the organ from future ischemic insults. It is shown that EPO mediates preconditioning by limiting the toxic effects of tumor necrosis factor-α and other inflammatory cytokines in the brain, heart, kidney, and other tissues. The authors also show that EPO production is suppressed by injury, raising the question of its use as a therapeutic agent in a variety of ischemic and other situations. They review the recent preclinical and clinical trials of exogenous EPO in ischemia–reperfusion and toxin-induced renal injuries, and in human stroke. Given that the therapy with EPO in experimental models was effective when given before or after the insult, there is a real hope for its effective use in human disease. Whether the signaling mechanism mediating the therapeutic effect is the same as that for erythropoeisis remains to be discovered. Information on the existence of EPO receptor isoforms is being established, including a possible tissue-protective receptor complex consisting of the EPO receptor and a co-receptor (CD131) that is also used by granulocyte–macrophage colony-stimulating factor, interleukin-3, and interleukin-5. Successfully engineered analogues of EPO that selectively activate tissue protection without stimulating hematopoiesis confirm the concept of a tissue-protective receptor and have significant potential utility in investigational and therapeutic arenas. **See page 246.**